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Biomolecular Homochirality

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1 Introduction

The absence of chiral symmetry in nature was first recognized by the discovery of the mirror-image distinction of enantiomeric molecules and the finding that one of the two optical isomers generally predominates in most organic natural products. The appreciation of chiral complementation between enantiomers was confined to overall morphological features initially, the extension to structural details following a quarter of a century later. Chemical science developed a theory of three-dimensional molecular structure only after 1874, when Le Bel[1] and van't Hoff[2] independently proposed that the four valencies of the carbon atom are directed towards the vertices of an atom-centred tetrahedron. The new proposal gave precision and a predictive potential to the earlier idea of molecular dissymmetry, due to Pasteur (1848), referring to the overall left- or right-handed shape of the molecule. Pasteur's conception of dissymmetry[3] derived from the general morphological principle of the crystallographer Haüy,[4] who postulated in 1809, from crystal cleavage observations, that a crystal and each constituent space-filling molecule are 'images of each other' in overall shape. The prevalence of only one of the two mirror-image enantiomers among natural organic products led Pasteur to postulate, and search for, the dissymmetric forces of nature.

2 Molecular Dissymmetry

The extension of Haüy's morphological analogy to the physical and chemical properties of substances resulted in Mitscherlich's (1819) law of isomorphism,[5] which linked similarity of crystal shape to an equivalence in stoicheiometric chemical composition, and the connection made by Herschel[6] in 1822 between the morphological handedness of quartz crystals and the sign of the crystal

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[1] J. A. Le Bel, 'Sur les relations qui existent entre les formules atomiques des corps organiques, et le pouvoir rotatoire de leurs dissolutions', *Bull. Soc. Chim. Fr.*, 1874, [2]**22**, 337—347.

[2] J. H. van't Hoff, 'Sur les formules de structure dans l'espace', *Arch. Neerl. Sci. Exactes Nat.*, 1874, **9**, 445—454.

[3] L. Pasteur, 'Mémoire sur la relation qui peut exister entre la forme crystalline et la composition chimique, et sur la cause de la polarisation rotatoire', *C. R. Acad. Sci. Paris*, 1848, **26**, 535—538.

[4] R. J. Haüy, 'Tableau Comparatif des Résultats de la Cristallographie et de l'Analyse Chimique relativement a la Classification des Minéraux', Paris, 1809, p. xvii.

[5] E. Mitscherlich, 'Ueber die Krystallization der Salze, in denen das Metall der Basis mit zwei Proportionen Sauerstoff verbunden ist', *Abh. König Preuss Akad. Wiss. Berlin*, 1819, 427—437.

[6] J. W. F. Herschel, 'On the Rotation Impressed by Plates of Rock Crystal on the Planes of Polarization of the Rays of Light as Connected with Certain Peculiarities in its Crystallization, *Trans. Cambridge Philos. Soc.*, 1822, **1**, 43—50.

optical activity. Quartz crystals divide into two enantiomorphous sets distinguished by the right- or the left-handed screw sequence of hemihedral facets that reduce the crystal symmetry from hexagonal to trigonal. Herschel found that all crystals of the left-handed morphological set are laevorotatory, while those of the right-handed set are dextrorotatory, producing a respective anticlockwise or clockwise rotation of the plane of polarized light propagated along the trigonal crystal axis. Herschel supposed that the particular morphological chirality of a quartz crystal and the sign of its optical activity had a common molecular basis, the supposition being developed and generalized by Fresnel in 1824. Fresnel[7] showed that optically-active substances have a circular birefringence, $(n_L - n_R)$, positive for dextrorotatory and negative for laevorotatory media, where n_L and n_R refer to the refractive indices for left- and right-circularly polarized light, respectively. Arguing by analogy, Fresnel proposed that the molecules of an optically-active medium have a left- or right-handed helical form or arrangement, like the envelope traced out by the oscillating vector of a circularly-polarized light wave.

The work of Herschel and Fresnel enabled Pasteur to resolve the apparent paradox, reported by Mitscherlich[8] in 1844, that the sodium ammonium salts of active (+)-tartaric acid and inactive racemic or paratartaric acid appear to be isomorphous and identical in all respects save optical activity. Repeating the crystallization of the inactive racemic salt, Pasteur[3] obtained two sets of hemihedral crystals, related morphologically as non-superposable mirror-image forms, like the two sets of quartz crystals. One set proved to be truly isomorphous with the crystals of the corresponding natural (+)-tartrate and to have an identical specific optical rotation in solution, positive in sign. In addition to the enantiomorphous crystal facets, the other set possessed a specific optical rotation of the same magnitude but negative in sign. From Haüy's morphological analogy principle, Pasteur inferred that the individual molecules of (+)- and (−)-tartaric acid are stereochemically dissymmetric, related as non-superposable mirror-image forms, like the macroscopic crystals of the corresponding sodium ammonium salts.

Optically-active substances in Pasteur's time were confined to natural products and their derivatives. Pasteur supposed that the laboratory syntheses of chiral compounds from achiral starting materials invariably produced racemic mixtures of enantiomers because chemists had not yet identified and employed the chiral forces of nature operating in both the organic and the inorganic world.[9] The solar system as a whole is dissymmetric, Pasteur observed, for it is not superposable on its mirror image, and so spin and orbital rotational forces may provide a basis for chiral structures; or magnetism, since Faraday[10] had shown

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[7] A. Fresnel, 'Considérations théoriques sur la polarisation de la lumière', *Bull. Sci. Soc. Philomath.*, 1824, 147–158.

[8] J. B. Biot, 'Communication d'une note de M. Mitscherlich', *C. R. Acad. Sci. Paris*, 1844, **19**, 719.

[9] L. Pasteur, 'La dissymétrie moléculaire', *Rev. Sci.*, 1884, [3] **VII**, 2–6.

[10] M. Faraday, 'On the magnetisation of light and the illumination of magnetic lines of force', *Philos. Mag.*, 1846, **28**, 294.

in 1846 that a magnetic field induces optical activity in glass and other isotropic transparent media. In this 1883 address to the Paris Chemical Society, Pasteur[9] described the several unsuccessful attempts he had made earlier to harness what he had taken to be the chiral forces of nature.

3 Chiral Synthesis

Pasteur's conjecture that chiral forces are inherent to the physical and organic world found few early supporters, and the work of Emil Fischer on the sugar series in the 1890's appeared to show that such forces are not needed to account for the homochirality of natural products. Fischer tested, and came to use as a guide,[11,12] van't Hoff's predictions[2] of the number and type of stereoisomers expected for a chain of n chiral carbon atoms, $R–(CXY)_n–R'$, with a tetrahedral orientation of the four bonds to each carbon atom, both for $R = R'$ with n even and for $R \neq R'$ for any integral value of n. Fischer himself supplied the expectation for $R = R'$ with n odd.[11] On increasing the value of n in the step-wise ascent of the aldose sugar series through Kiliani's cyanohydrin reaction, Fischer found the synthesis to be stereoselective, the yields of the two diastereomers produced from a given lower sugar being markedly unequal. The action of enzyme preparations proved to be stereospecific. Maltase and emulsin cleave solely the α- and the β-D-glucosides, respectively, and both enzymes are without effect on either of the corresponding L-glucoside series or other L- or D-aldose series.

Such observations led Fischer to propose his stereochemical 'key and lock' hypothesis, designed to provide 'a simple solution to the enigma of natural asymmetric synthesis'.[12] Starting with a single enantiomer or even with an enantiomeric excess in a mixture of optical isomers, synthetic reactions lead inevitably to a dominant diastereomeric product favoured by the steric congruence of the reaction intermediates. Neither a *vis vitalis* nor Pasteur's physical chiral force of nature external to the organism are required to account for the predominance, characterized by Fischer, of the D-series of sugars and the L-series of α-amino acids in the homochiral biochemistry of living organisms. Chiral homogeneity is the precondition for an economic and efficient metabolic turnover and biosynthesis in stereochemical 'key and lock' terms, like the universal adoption of right-handed nuts and bolts or screws in engineering for industrial efficiency and economy.

4 Chiral Fields

The 'key and lock' hypothesis left unexplained the origin of the initial prebiotic substance or enantiomeric excess, as Fischer himself appreciated.[12] One solution, still sustained,[13] relegates the initial choice to 'chance', a general synonym for causes as yet unknown or even deemed unknowable. The particular selection of the D-sugars and the L-amino acids during the course of biochemical evolution

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[11] E. Fischer, 'Ueber die Configuration des Traubenzuckers und seiner Isomerism, *Ber. Dtsch. Chem. Ges.*, 1891, **24**, 2683—2687.

[12] E. Fischer, 'Synthesen in der Zuckergruppe', *Ber. Dtsch. Chem. Ges.*, 1894, **27**, 3189—3232.

[13] A. G. Cairns-Smith, 'Chirality and the Common Ancestor Effect', *Chem. Brit.*, 1986, **22**, 559 561.

appears to be a 'frozen accident', propagated by the 'common ancestor' effect. Another approach went back to Pasteur, re-examining the forces of nature which he had taken to be dissymmetric. Pierre Curie showed in 1894 that while both an electric field and a magnetic field have a mirror plane of symmetry individually, these planes are eliminated in collinear combinations of the two fields.[14] There are two enantiomorphous chiral combinations, one in which the electric and the magnetic field are parallel, and the other where the component fields are antiparallel. If the electric and the magnetic field oscillate at the same frequency, the two chiral combinations represent right- and left-hand circularly polarized electromagnetic radiation.

Curie's analysis rationalized the earlier surmise of Le Bel[1] that circularly polarized light provides a chiral force 'which favours the formation of one of the dissymmetric isomers' in photochemical reactions, and it supported a model of the relationship between the handedness of a chiral molecule and its optical activity put forward by Drude.[15]

Drude proposed that the interaction of a chiral molecule with the electromagnetic radiation field gives rise to a helical charge displacement in the molecule. Dependent upon the handedness of the molecular structure, the oscillatory charge displacement at a resonant radiation wavelength has a right-handed helical form in one optical isomer, and left-handed in the enantiomer. The electric and the magnetic dipole moments induced in the molecule are parallel for the right-handed helical charge displacement, or antiparallel for the corresponding enantiomeric displacement, resulting in a respective positive or negative circular dichroism light absorption ($\Delta\varepsilon = \varepsilon_L - \varepsilon_R$) at the resonant light wavelength, and a corresponding circular birefringence (respective dextrorotation or laevorotation) at longer wavelengths in the transparent spectral region. The differential absorption of left- and right-circularly polarized light by chiral substances, circular dichroism, was first observed for axial propagation in amethyst quartz crystals[16] and subsequently (1895) for general propagation directions in isotropic solutions of copper(II) and chromium(III) (+)-tartrate by Cotton.[17]

Le Bel's early surmise, strengthened by Drude's theory of optical activity, Curie's characterization of chiral fields, and Cotton's discovery of circular dichroism in fluid phases, led Byk[18] to suggest in 1905 that biomolecular chiral homogeneity had a photochemical origin. It was assumed by Byk, and by other workers over the following half-century,[19] that there is a natural predominance of one of the two circularly polarized components of the solar radiation reaching

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[14] P. Curie, 'Sur la symétrie dans les phénomènes physiques', *J. Phys.*, 1894, [3] **III**, 393—416.

[15] P. Drude, 'The Theory of Optics', (1900), (trans. C. R. Mann and R. A. Millikan), Dover reprint, New York, 1959, pp. 400—417.

[16] T. M. Lowry, 'Optical Rotatory Power', Longmans Green, London, 1935, p. 149.

[17] A. Cotton, 'Recherches sur l'absorption et la dispersion de la lumière par les milieux doués du pouvoir rotatoire', *C. R. Acad. Sci. Paris*, 1895, **120**, 989.

[18] A. Byk, 'Zur Frage der Spaltbarkeit von Racemverbindungen durch circular-polarisiertes Licht, ein Beitrag zur Primärentstehung optisch-activer Substanz', *Ber. Dtsch. Chem. Ges.*, 1905, **37**, 4696—4700.

[19] W. A. Bonner, 'Origins of molecular chirality', in 'Exobiology', ed. C. Ponnamperuma, North-Holland Publishing Co., Amsterdam, 1972, pp. 170—234.

the Earth's surface, generally the right-circular component. Recent measurements show that the solar radiation has indeed a circular polarization of up to 0.5% over the visible, near infrared, and near ultraviolet regions at twilight, owing to multiple aerosol scattering.[20] The net effect is very small, however, the right-circular component in excess at sunrise being nearly equal in magnitude but opposite in sign to the left-circular component in excess at sunset. Similarly the excess of right-circular light from the north pole of the Sun is almost cancelled by the excess of left-circular radiation from the south pole.[21] The net excess of right-circular polarization in the radiation from the Sun lies at the one part per million level and it is broad-band, covering the whole photochemically-active wavelength range.[21] An enantioselective photosynthesis or photolysis requires the irradiation of a racemic mixture with monochromatic circularly polarized light at the wavelength corresponding to a particular circular dichroism absorption band, so that one enantiomer absorbs more radiation and undergoes more photochemical change than the other. In the circular dichroism spectrum of an enantiomer the CD bands or band-systems alternate in sign along the wavelength ordinate and the sum of the frequency-weighted CD band areas vanishes over the spectrum as a whole. Thus the broad-band irradiation of a racemic substance with left- or right-circularly polarized light produces racemic photoproducts with no enantioselection.

On a time and a space average, the electromagnetic and other classical chiral fields characterized by Curie are even-handed, and it is necessary to postulate a particular time or place, or narrow-band circularly polarized irradiation, for the origin of biomolecular chiral homogeneity through their agency. Thus a racemic pool of α-amino acids located on an east-facing slope, and so exposed preferentially to the right-circular excess of solar radiation at sunrise, over the short-wavelength tail of the quartz ultraviolet region remaining from the atmospheric absorption of sunlight prior to the development of an ozone layer, would be expected to undergo enantioselective photolysis, leaving the L-isomer in excess, from reports of the asymmetric photolysis of racemic amino acids with circularly polarized radiation in the 200—230 nm region.[22,23]

5 Parity and its Non-conservation

The apparent even-handedness of the established forces of nature became generalized as the principle of the conservation of parity by Wigner[24] in 1927. All physical causes and the laws linking them to the effects produced, Wigner

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[20] R. D. Wolstencroft, 'Astronomical sources of circularly polarized light and their role in determining molecular chirality on Earth', in 'The Search for Extraterrestrial Life: Recent Developments', ed. M. D. Papagiannis, IAU Symposium 112, Reidel, Dordrecht, 1985, pp. 171—175.

[21] J. C. Kemp, G. D. Henson, C. T. Steiner, and E. R. Powell, 'The optical polarization of the Sun measured at a sensitivity of parts in ten million', *Nature (London)*, 1987, **326**, 270—273.

[22] J. J. Flores, W. A. Bonner, and G. A. Massey, 'Asymmetric Photolysis of (*RS*)-Leucine with Circularly Polarized Ultraviolet Light', *J. Am. Chem. Soc.*, 1977, **99**, 3622—3625.

[23] B. Norden, 'Was photoresolution of amino acids the origin of optical activity in life?', *Nature (London)*, 1977, **266**, 567–568.

[24] E. Wigner, 'Einige Folgerungen aus der Schrödingerschen Theorie für die Termstrukturen', *Z. Phys.*, 1927, **43**, 624—652.

proposed, are invariant to space-inversion (the parity operation) or, what is equivalent, to mirror-plane reflection. For the following thirty years it was assumed that the principle of parity conservation applied not only to the classical gravitational and electromagnetic interaction but also to the new strong and weak nuclear interaction, mediating α- and β-radioactivity, respectively. The use of β-emitting radionucleides as beam sources for electron polarization and scattering studies (1928—30) gave results which, at least in retrospect, provided evidence for parity violation in the weak interaction.[25] But these results were set aside and were forgotten until the accumulation of other anomalies led Lee and Yang[26] to conclude in 1956 that parity is not conserved in the weak interaction.

The observation of the parity-violating effects predicted by Lee and Yang showed that the fundamental particles have an intrinsic handedness or helicity. In the β-decay of radionucleides, the electrons emitted are inherently left-handed, with their spin-axis preferrentially orientated antiparallel to the direction of their linear momentum, while positrons emitted in β-decay are intrinsically right-handed, with a parallel alignment of spin-axis and momentum direction.[27] Although parity itself is not conserved in the weak interaction, the combination of parity (P) with charge-conjugation (C), the conversion of a particle into the corresponding antiparticle, *e.g.* the conversion of an electron into a positron, is conserved in good approximation (strictly, time-reversal T must be included to give the more exact principle of CPT conservation). According to the principle of CP conservation, the electron and the positron are CP mirror-image forms, and a chiral molecule composed of electrons and other particles, *e.g.* L-alanine, has a true CP mirror-image D-enantiomer, with equivalent properties, made up of positrons and other antiparticles in a counter-world of antimatter. But the natural enantiomer, *i.e.* D-alanine with the standard particle composition, has properties dependent upon the weak interaction which are inequivalent.

The first inequivalence investigated was the differential decomposition of the two enantiomers in a racemic mixture expected from β-irradiation, due either to the direct competitive radiolysis of the optical isomers by the β-electrons, or to the indirect differential photolysis arising from the left-circularly polarized braking radiation (Bremsstrahlung) produced as the β-electrons slow down from their initial relativistic velocities on emission in the β-decay.[28] As yet, no reproducible enantioselective reactions have been reported from such investigations, or from the use of spin-polarized electrons, positrons, or protons produced by particle accelerators.[29,30]

[25] A. Franklin, 'The Discovery and Nondiscovery of Parity Nonconservation', *Stud. Hist. Philos. Sci.*, 1979, **10**, 201—257.

[26] T. D. Lee and C. N. Yang, 'Question of Parity Conservation in Weak Interactions', *Phys. Rev.*, 1956, **104**, 254—258.

[27] C. S. Wu, E. Ambler, R. W. Hayward, D. D. Hoppes, and R. P. Hudson, 'Experimental Test of Parity Conservation in Beta Decay', *Phys. Rev.*, 1957, **105**, 1413—1415.

[28] T. L. V. Ulbricht and F. Vester, 'Attempts to induce optical activity with polarized β-radiation, *Tetrahedron*, 1962, **18**, 629—637.

[29] W. A. Bonner, 'Experimental evidence for β-decay as a source of chirality by enantiomer analysis', *Origins of Life*, 1984, **14**, 383—390.

[30] J. Van House, A. Rich, and P. W. Zitzewitz, 'Beta decay and the origin of biological chirality: new experimental results', *Origins of Life*, 1984, **14**, 413—420.

The expected effect is small. It is estimated that the maximum enantiomeric excess [(L − D)/(L + D)] produced prebiotically by the action of natural terrestrial β-radioactivity on racemic mixtures of organic substances has a 10^{-12} order of magnitude at most,[31] and an extension of the analysis further reduces the expected magnitude-order.[32] The effect is small because the handedness of a β-electron or β-positron is substantial only at high energies ($>10^6$ electron volt) where the velocity of the particle approaches the speed of light. The handedness (helicity) of a β-electron and the circular polarization of the associated braking radiation are vanishingly small at the energies (2—5 electron volt) of the molecular valency electron changes involved in stereoselective chemical reactions. Moreover, the Kuhn–Condon sum rule for rotational strengths indicates that broad-band polarized photolysis or radiolysis lacks chiral discrimination: monochromatic resonant radiation is essential for photochemical enantiodifferentiation.

6 The Electroweak Interaction

The β-decay of radionucleides, involving charge changes, is governed by the weak charged current (WCC) mediated by the charged massive bosons, $W^{\pm}$, of the weak interaction, and WCC parity-violating effects vanish in the non-relativistic limit of low energies. During the 1960's, the electromagnetic and the weak nuclear interaction were unified into the electroweak interaction,[33] dependent upon the weak neutral current (WNC) mediated by the massive neutral boson, Z^0, which was detected, along with its charged counterparts, $W^{\pm}$, at CERN in 1983.[34] The parity-violating effects of the electroweak WNC interaction, in contrast to those of the WCC interaction, remain finite in the low-energy non-relativistic limit, and they have significance for the stationary as well as the transitional electronic states of atoms and molecules.

From the electroweak viewpoint, a spherically-symmetric atom, composed of particles, is a chiral system with a CP enantiomer made up of the corresponding antiparticles, and a free atom is expected to exhibit optical activity. The optical activity, although small, increases in approximate proportion to Z^6, where Z is the atomic number. Measurements of the optical rotation of heavy metal vapours, bismuth, lead, thallium, and caesium, give an optical activity in agreement with the calculated sign and magnitude, which is smaller by some 10^{-4} than that typical of a chiral molecule.[35,36] Since the natural enantiomers of a chiral molecule differ only in the spatial arrangement of the atoms they possess in

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[31] R. A. Hegstrom, 'Weak neutral current and β-radiolysis effects on the origin of biomolecular chirality', *Nature* (*London*), 1985, **315**, 749—750.

[32] W. J. Meiring, 'Nuclear β-decay and the origin of biomolecular chirality', *Nature* (*London*), 1987, **329**, 712—714.

[33] Nobel lectures, *Rev. Mod. Phys.*, 1980, **52**: S. Weinberg, 'Conceptual foundations of the unified theory of weak and electromagnetic interactions', 515—523; A. Salam, 'Gauge unification of fundamental forces', 525—538; S. L. Glashow, 'Towards a unified theory: Threads in a tapestry', 539—543.

[34] R. Walgate, 'What will come after Z^0?', *Nature* (*London*), 1983, **303**, 473.

[35] T. P. Emmons, J. M. Reeves, and E. N. Fortson, 'Parity-nonconserving optical rotation in atomic lead', *Phys. Rev. Lett.*, 1983, **51**, 2089—2092; and 1984, **52**, 86.

[36] M.-A. Bouchiat and L. Pottier, 'Optical Experiments and Weak Interactions', *Science*, 1986, **234**, 1203—1210.

common, the electroweak optical activity of the constituent atoms produces an optical molecular inequivalence, adding to the molecular optical activity of one enantiomer and subtracting from that of the other. Thus a minor enantioselection is expected in the photolysis of a racemate, even with radiation lacking a net polarization (equal numbers of left- and right-circularly polarized photons).

Similarly the electroweak interaction discriminates between the binding energy of corresponding electronic states, stationary or transitional, of the two mirror-image forms of a chiral molecule. A small electroweak energy increment, E_{ew}, is added to the binding energy of a given electronic state in one enantiomer and subtracts from that of the corresponding state in the other, giving an electroweak binding energy difference between the two optical isomers ($\Delta E_{ew} = 2|E_{ew}|$). The inclusion of the electroweak interaction in *ab initio* calculations of the ground-state electronic binding energy of salient biomolecules indicates that the particular enantiomers selected during the course of biochemical evolution are, in fact, those which are preferentially stabilized relative to their mirror image forms by the WNC interaction.

The peptide unit of a L-polypeptide in either the regular α-helix or the pleated β-sheet conformation, and the parent L-α-amino acids with the conformation preferred in aqueous solution, are slightly more stable than their respective D-enantiomers in the ground state.[37,38] Similarly, it turns out that the parent D-aldotriose, in the form of hydrated D-(+)-glyceraldehyde with its preferred solution conformation, is energetically stabilized relative to its L-enantiomer in the ground state,[39] and so too is the biologically important furanose, D-ribose, in either of its preferred envelope conformations, C(2)-*endo* or C(3)-*endo*.[40] In all of these cases, the electroweak enantiomeric energy difference, ΔE_{ew}, amounts to no more than $\sim 10^{-14}$ J mol^{-1}, corresponding to an excess of about 10^6 molecules of the stabilized enantiomer per mol of racemate in thermodynamic equilibrium at Earth-surface temperature. The ratio of the enantiomeric energy difference to the thermal energy at 300 K, ($\Delta E_{ew}/kT \sim 10^{-17}$), provides a measure of the enantiomeric energy advantage relative to ambient thermal fluctuations at the level of the individual dissymmetric molecule, the chiral monomer residue of a polymer, or the unit cell of an enantiomorphous crystal, composed of the lighter elements.

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[37] S. F. Mason and G. E. Tranter, 'The parity-violating energy difference between enantiomeric molecules', *Mol. Phys.*, 1984, **53**, 1091—1111; 'The electroweak origin of biomolecular handedness', *Proc. R. Soc. London, A*, 1985, **397**, 45–65.

[38] G. E. Tranter 'The parity-violating energy differences between the enantiomers of α-amino acids', *Mol. Phys.*, 1985, **56**, 825–838.

[39] G. E. Tranter, 'Preferential stabilisation of the D-sugar series by the parity-violating weak interactions', *J. Chem. Soc., Chem. Commun.*, 1986, 60—61.

[40] G. E. Tranter, 'The enantio-preferential stabilization of D-ribose from parity violation, *Chem. Phys. Lett.*, 1987, **135**, 279–282.

7 Chiral Amplification

Although small, the electroweak interaction has provided a universal and uniform natural background bias from the 'first three minutes' and beyond, throughout the history of the Earth, constant in time and equivalent in the two hemispheres, unlike the classical chiral fields with a handedness dependent upon particular times and places. To a degree, Pasteur's conjecture is now vindicated,[41] although the chiral force of nature has not the magnitude he envisaged. Current forms of Fischer's 'key and lock' mechanism for stereochemical discrimination between alternative products in diastereomer formation account well for the long-term development of biomolecular chiral homogeneity, given a sufficient initial enantiomeric excess, but it seems unlikely that the small enantiomeric advantage ratios provided by the electroweak interaction or selective β-radiolysis at the single-molecule level are adequate without some preliminary enhancement.

Two main types of chiral amplification have been proposed, involving either a sudden catastrophic change from racemic to homochiral chemical kinetics or a gradual cumulative evolution to chiral homogeneity. A general mechanism of the former type was first put forward by Frank[42] in 1953 and it has been developed in detail recently in order to assess the significance of the electroweak enantiomeric energy difference for chiral biomolecules.[43] The kinetic processes are Darwinian in form with each enantiomer acting as 'a catalyst for its own production and an anticatalyst for the production of its optical antimer'.[42]

The catastrophic mechanism envisages an open flow-reactor system, such as a lake, fed by an input of achiral substrates, A and B, with a steady state maintained in the flow-reactor by an output of the enantiomers X_L and X_D produced, together with inactive products, P. Each optical isomer autocatalyses its own production from the achiral substrates and inhibits the production of its enantiomer by combining with the latter irreversibly to form the inactive products. The dynamic steady-state in the reactor remains stable so long as the input concentration of the substrates remains small, and the output of the chiral products is racemic, equimolecular in X_L and X_D, with an equal contribution from each of the two competing autocatalytic reaction processes. As the input concentration of the substrates increases, a critical point is reached where the steady state becomes metastable and hypersensitive to minor inequalities between the activation parameters, or between the stationary concentrations, of corresponding enantiomeric intermediates in the two homochiral reaction branches. Under the critical conditions producing metastability, the system switches to the chirally-homogeneous reaction branch favoured by the minor inequalities, unless the thermal fluctuations are large enough to damp out the transition, or to reverse it adventiously to the disfavoured homochiral reaction channel.

In the original Frank mechanism,[42] formulated before the discovery of parity non-conservation in the weak interaction, the activation parameters and stationary

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[41] J. B. S. Haldane, 'Pasteur and Cosmic Asymmetry', *Nature* (*London*), 1960, **185**, 87.

[42] F. C. Frank, 'On spontaneous asymmetric synthesis', *Biochim. Biophys. Acta*, 1953, **11**, 459—463.

[43] D. K. Kondepudi and G. W. Nelson, 'Weak neutral currents and the origin of biomolecular chirality', *Nature* (*London*), 1985, **314**, 438—441.

concentrations of corresponding enantiomeric intermediates in the two reaction sequences were taken to be equal, and the choice of the particular homochiral reaction branch adopted under the critical conditions of hypersensitive metastability was accordingly a matter of chance, with an equal probability for each of the two sequences. The particular handedness of biochemical chiral homogeneity, the L-amino acids and the D-sugars, thus appeared to be the outcome of a 'frozen accident', arising from a consolidation of the initial random choice through subsequent chemical elaborations of the open flow-reactor system from autocatalysis to membrane-enclosed self-replication. This now-old viewpoint still retains a few supporters.[13,44]

The assumption that the concentrations of corresponding intermediates, and their activation parameters, in the two enantiomeric reaction branches are equal became untenable after the evaluation of the electroweak enantiomeric inequivalencies. A recent quantitative analysis of the autocatalysed competitive reaction sequences in the Frank mechanism shows that, at the critical point where racemic production becomes metastable, the choice of the particular homochiral reaction branch adopted becomes determinate if corresponding enantiomeric intermediates in the two branches differ in relative concentration by the excess, $[(\mathrm{L} - \mathrm{D})/(\mathrm{L} + \mathrm{D})] > 10^{-17}$, or, equivalently, differ in activation energy by ΔE, such that $(\Delta E/kT) > 10^{-17}$.[43] The lower limit of the condition is satisfied by the enantiomeric excess due to the electroweak interaction at 300 K evaluated for the D-sugars studied,[39,40] the L-α-amino acids and the L-peptide moiety in the α-helix or the β-sheet conformation.[37,38] A computer simulation of the open flow-reactor system, with typical rate constants for the elementary kinetic stages of the Frank mechanism, indicates that, at the lower limit of the selection condition, the energetically favoured enantiomeric series is selected with 98% probability if the passage through the critical metastable stage occupies some 10^4 years, during which the input concentration of the substrate increases by 10^{-3} to 10^{-2} molar in a reservoir of some 4×10^9 litre capacity, corresponding to a lake one kilometre in diameter and four metres deep.[43]

Cumulative mechanisms for chiral amplification are more complementary than opposed to the catastrophic mechanisms. Preceded by a cumulative enhancement of the electroweak enantiomeric excess, the bifurcation catastrophe of the Frank mechanism, from racemic production to one of the two enantiomeric branches, is expected to require less restrictive conditions, a shorter time interval for the critical transition, a smaller flow-reactor volume, and more latitude in other variable factors.

An early and typical cumulative mechanism envisaged an enhancement of the enantiomeric excess or the differential stabilization energy of a chiral monomer on condensation, the amplification being proportional to the degree of polymerization.[45] The proportionality holds only if the polymer is chirally homogeneous.

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[44] V. I. Goldanskii and V. V. Kuz'min, 'Spontaneous Mirror Symmetry Breaking in Nature and the Origin of Life', *Z. Phys. Chem. (Leipzig)*, 1988, **269**, 216–274.

[45] Y. Yamagata, 'A Hypothesis for the Asymmetric Appearance of Biomolecules on Earth', *J. Theor. Biol.*, 1966, **11**, 495–498.

The polymerization of the *N*-carboxy anhydride derivative of a near-racemic α-amino acid does not afford a chirally homogeneous product but, if the polymerization is partial (~50%), the initial enantiomeric excess is enhanced by some 3—14% in the polymer formed, dependent upon the conditions and the particular amino acid. If the polymer produced is partly hydrolysed (~50%), an additional and comparable optical enrichment is found in the residual polymer, while the monomer from the hydrolysis, like the monomer remaining from the partial polymerization, becomes optically depleted and closer to the racemic composition.[46]

The condition of chiral homogeneity over the units of the aggregate as a whole is satisfied by an enantiomorphous crystal built up from a chiral unit cell, as in the case of quartz. The terrestrial distribution of quartz crystals, documented for a total of 17 738 crystals collected from a variety of locations, suggests a global bias with an enantiomeric excess of 1.4% of the morphologically left-handed (−)-quartz form, significant at the 1.9 standard deviation level.[47–49] In some localities, *e.g.* the Samshvil'do region in the U.S.S.R., the left-bias of the quartz crystal distribution appears to be larger than that globally: a least-squares analysis of the chiral distribution over sets totalling 4000 quartz crystals from this region was found to minimize at the level of a 2.4% enantiomeric excess of the L-(−)-quartz form.[48] In contrast, a similar analysis of sets totalling 1459 quartz crystals from Algeria minimized to near-racemic distribution, with 716 L-forms, 702 D-forms, and 41 L/D Brazilian-type twin-crystals.[49]

The electroweak stabilization of the unit cell of L-(−)-quartz relative to that of the D-(+)-enantiomorph amounts to the ~300 K advantage ratio, $(\Delta E_{ew}/kT) \sim 10^{-17}$, typical of chiral atomic assemblies of the lighter elements. The global 1.4% enantiomeric excess of the L-(−)-enantiomorph corresponds, according to the cumulative chiral amplification mechanism, to an aggregate of some 10^{15} units cells, which are contained in a macroscopic single crystal with dimensions of ~0.1 mm along each main edge.[37,50] A larger enantiomeric excess is expected for chiral crystals containing heavier elements, since the electroweak energy difference between enantiomers is predicted to be proportional to $\sim Z^5$, or to an even higher power of the atomic number according to recent relativistic evaluations.[51] In the case of sodium uranyl acetate which, like quartz, is achiral

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[46] N. E. Blair and W. A. Bonner, 'Experiments on the amplification of optical activity', *Origins of Life*, 1980, **10**, 255—263.

[47] C. Palache, H. Berman, and C. Frondel, 'Dana's System of Mineralogy', 7th Edn., Vol. III, John Wiley, New York, 1962, p. 16.

[48] A. B. Vistelius, 'On the Populations of the Enantiomorphs of Quartz', *Mem. Russ. Mineral Soc.*, 1950, **79**, 191—195 (in Russian).

[49] P. Bussiere and J. Maisonneuve, 'Repartition des variétés enantiomorphes du quartz dans les granites de la Tefedest (Hoggar-Algerie)', *Travaux du Laboratoire de Géologie et Minéralogie de l'Université de Clermont-Ferrand*, No. 18, 1971, 1—25.

[50] G. E. Tranter, 'Parity-violating energy differences of chiral minerals and the origin of biomolecular homochirality', *Nature* (*London*), 1985, **318**, 172—173.

[51] L. Wiesenfeld, 'Effect of atomic number on parity-violating energy differences between enantiomers', *Mol. Phys.*, 1988, **64**, 739—745.

in the fluid phase and forms enantiomorphous crystals (space group $P2_13$), the enantiomeric excess over a total of 3596 crystals of those with a positive circular intensity difference in their luminescence amounts to 6.8‰ on a number basis or 3.4‰ on a weight basis.[52]

The terrestrial enantiomeric excess of (−)-quartz has implications for the natural optical enrichment of organic biomolecules. Finely powdered (−)-quartz preferentially absorbs L-alanine from solutions of racemic alanine hydrochloride with a fractional enantiomeric excess of 1—20‰, dependent upon the particular conditions.[53] The enantioselective adsorption, taken in conjunction with the 1.4‰ global mean fractional dominance of (−)-quartz crystals, gives L-alanine an enantiomeric excess, or an equivalent energy advantage at ambient temperature ($\Delta E/kT$) over its D-enantiomer, of $>10^{-4}$ for subsequent physical or chemical processes mediated by the crystal surface.[50]

An enantiomeric excess of $\sim 10^{-4}$ provides a reasonable starting point for subsequent optical enrichment by sequences of partial polymerization and incomplete polymer-hydrolysis. Equally an enantiomeric advantage ratio of $\sim 10^{-4}$ at ambient temperature allows a brief passage through the critical bifurcation transition from racemate to enantiomer production by the Frank mechanism, in a flow-reactor of modest capacity, and thus plausibly uniform and homogeneous in reactant composition and reaction rate throughout its volume.[43] Given prebiotic seasonal variations comparable to those today, uniform reaction conditions, slowly changing over 10^4 years in a flow-reactor of 4×10^9 litre capacity, appear to be unrealistically restrictive, but such conditions are required at the 10^{-17} level for the enantiomeric excess derived directly from the electroweak interaction at the single-molecule level. Some preliminary enhancement of the electroweak enantiomeric excess from the molecular level appears to be quantitatively essential. However, the qualitive result that the excess evaluated favours both the D-sugar and the L-amino acid series, including the regular conformations of the L-polypeptides, has a basic significance and fundamental consequence.

8 Universal Dissymmetry

The universe as a whole now appears to have less chiral symmetry and uniformity than was once supposed. The particles substantially outnumber their CP enantiomers, the antiparticles, and the chiral galaxies aggregate into non-racemic clusters and superclusters, all streaming towards a location defining the Great Attractor.[54] The cosmic dissymmetry perceived by Pasteur in his later years was confined to the solar system:[9] a century later the dissymmetry extends over the systems of galactic superclusters. Recent surveys of the winding direction of the spiral galaxies reveal a significant enantiomorphic excess of *S*-type

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[52] S. F. Mason, 'Biomolecular handedness from Pasteur to parity non-conservation', *Nouv. J. Chim.*, 1986, **10**, 739–747.

[53] S. Furuyama, M. Sawada, K. Hachiya, and T. Morimoto, 'Asymmetric Adsorption of Alanine by Quartz Powder from Ethanol Solution', *Bull. Chem. Soc. Jpn.*, 1982, **55**, 3394–3397.

[54] A. Dressler, 'The Large-Scale Streaming of Galaxies', *Sci. Am.*, 1987, **257**, (No. 3) 38–46.

anticlockwise rotation over Z-type clockwise rotation.[55–57] Taken in conjunction with the general translational galactic recession, the rotations specify the S-type as left-handed and the Z-type as right-handed. A general survey of 7563 galaxies finds a 4.6% fractional excess of S-rotational forms, corresponding to 4.9 standard deviations,[55] and a survey of the Local Supercluster reports a 9.8% fractional excess of the S-rotational types.[57] According to the standard Big Bang model, the particles outnumbered the antiparticles from an early stage, but galaxy formation began long after the primary separation of the electromagnetic from the weak interaction. The separation involved a phase transition, which may have been first-order and subject to supercooling with a separational delay,[58] conferring a left-handed preference upon the motions of the protogalaxies.

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[55] T. M. Borchkhadze and N. G. Kogoshvili, 'The Anisotropy of Spiral Galaxy Orientation', *Astron. Astrophys.*, 1976, **53**, 431—433.

[56] T. Yamagata, M. Hamabe, and M. Iye, 'Angular Momentum Orientation of Spiral Galaxies', *Tokyo Obs. Ann.*, 1981, **18**, 164—174.

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[58] S. Weinberg, 'The First Three Minutes', Fontana, London, 1983, pp. 139, 159.